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Patentanmeldung Nr. Patent application No. Demande de brevet n°

03007104.7

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Synergistic combination

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Synergistic combination

Field of application of the invention

The invention relates to the combination of certain known active compounds for therapeutic purposes. The substances used in the combination according to the invention are a known active compound from the PDE inhibitor class and active compounds from the anticholinergic agent class.

Prior art

International patent application WO02/069945 generally describes the combination of a compound from the class of PDE4 inhibitors with a compound from the class of anticholinergic agents for the treatment of respiratory tract disorders. International Patent application WO02/096463 describes an inhaled combination of a selective PDE4 inhibitor and an anticholinergic agent, with the proviso that the anticholinergic agent is not a tiotropium salt. International patent application WO02/096423 describes a combination of therapeutic agents useful in the treatment of obstructive airways and other inflammatory diseases comprising (I) a PDE4 inhibitor that is therapeutically effective in the treatment of said diseases when administered by inhalation; together with (II) an anticholinergic agent comprising a member selected from the group consisting of tiotropium and derivatives thereof that is therapeutically effective in the treatment of said diseases when administered by inhalation.

Summary of the invention

The invention relates to pharmaceutical compositions and methods for preventing or reducing the onset of symptoms of respiratory diseases, or treating or reducing the severity of respiratory diseases. In particular it relates to compositions and methods for treating respiratory diseases mediated by phosphodiesterase 4 (PDE4) by administering a PDE4 inhibitor together with another pharmaceutically active agent, which affects pulmonary function. In this connection, it is the object of the present invention to make available a certain respiratory tract therapeutic, which fulfills the following conditions:

- Pronounced antiinflammatory action
- Distinct bronchorelaxation and -dilatation
- Good bioavailability
- Minor side effects
- Good suitability for long-term therapy
- Favorable influence on bronchial hyperreactivity

It has now been found that the combined use of the PDE4 inhibitor roflumilast and an anticholinergic agent selected from the group of ipratropium, oxitropium and tiotropium salts outstandingly fulfills the abovementioned conditions, in particular in view of the fact that the combination of the compounds acts synergistically, i. e. exhibits a greater than additive effect.

Accordingly, the invention relates in a first aspect to a method for preventing or reducing the onset of symptoms of a respiratory disease, or treating or reducing the severity of a respiratory disease by administering to a patient in need thereof topically an effective amount of roflumilast and an anticholinergic agent selected from the group of ipratropium, oxitropium and tiotropium salts.

The invention also relates to a pharmaceutical composition suited for topical administration for preventing or reducing the onset of symptoms of a respiratory disease, or treating or reducing the severity of a respiratory disease, comprising an effective amount of roflumilast, an effective amount of an anticholinergic agent selected from the group of ipratropium, oxitropium and tiotropium salts, and a pharmaceutical acceptable excipient.

The invention additionally relates to a method for preparing a composition which is effective for preventing or reducing the onset of symptoms of a respiratory disease, or treating or reducing the severity of a respiratory disease, which method comprises mixing an effective amount of roflumilast and an anticholinergic agent selected from the group of ipratropium, oxitropium and tiotropium salts with a pharmaceutically acceptable excipient.

Detailed description of the invention

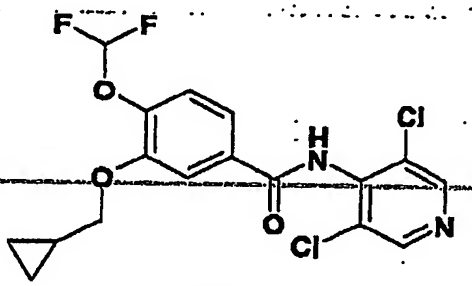
The combination therapy which is the subject matter of this invention comprises administering roflumilast with an anticholinergic agent selected from the group of ipratropium, oxitropium and tiotropium salts to prevent the onset of a respiratory disease event or to treat an existing condition. The two compounds are administered topically together in a single dosage form; or they are administered topically in two different dosage forms. They may be administered at the same time. Or they may be administered both close in time or remotely, such as where one drug is administered in the morning and the second drug is administered in the evening.

The combination may be used prophylactically or after the onset of symptoms has occurred. In some instances the combination may be used to prevent the progression of a respiratory disease or to arrest the decline of a function such as lung function.

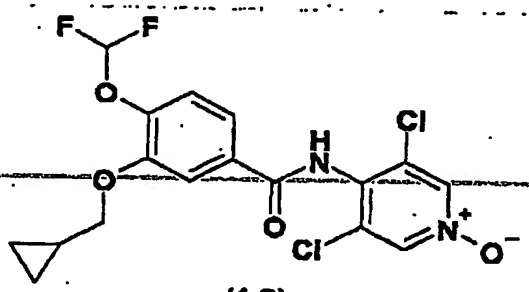
The invention thus relates to the combined use of roflumilast and an anticholinergic agent selected from the group of ipratropium, oxitropium or tiotropium salts, preferably ipratropium bromide, oxitropium bromide or tiotropium bromide in preventing the symptoms of, or treating a respiratory disease.

In the sense of the invention, the term "roflumilast" is understood to include the pharmaceutically acceptable salts and the N-oxide of ROFLUMILAST, which can likewise be used according to the invention.

ROFLUMILAST is the international non proprietory name (INN) for 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide [structure of formula (1.1)]. The preparation of 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide, its pharmaceutically acceptable salts and its N-oxide [3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloro-1-oxypyrid-4-yl)-benzamide; structure of formula (1.2)] as well as the use of these compounds as phosphodiesterase (PDE) 4 inhibitors is described in WO95/01338.



(1.1)

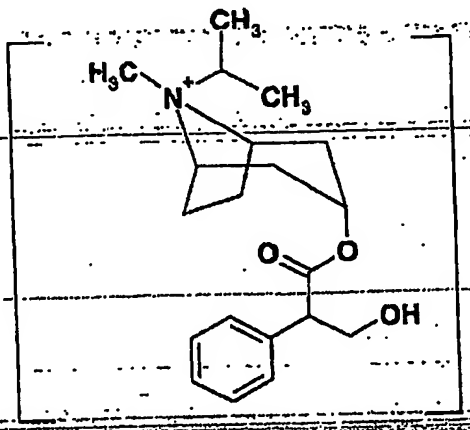


(1.2)

Suitable pharmaceutically acceptable salts of 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide (ROFLUMILAST) are in particular water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)-benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 1-hydroxy-2-naphthoic acid, the acids being employed in salt preparation – depending on whether it is a mono- or polybasic acid and depending on which salt is desired – in an equimolar quantitative ratio or one differing therefrom.

Anticholinergic agents suitable for use in the invention are ipratropium, oxitropium or tiotropium salts.

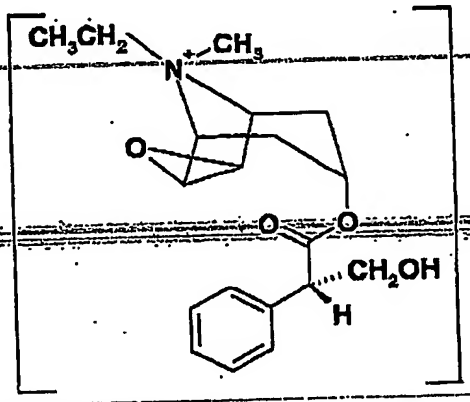
An ipratropium salt (see DE1670142) has the structure of formula (1.3)



(1.3)

wherein X is a pharmaceutically acceptable anion.

An oxitropium salt (see DE1795818) has the structure of formula (1.4):

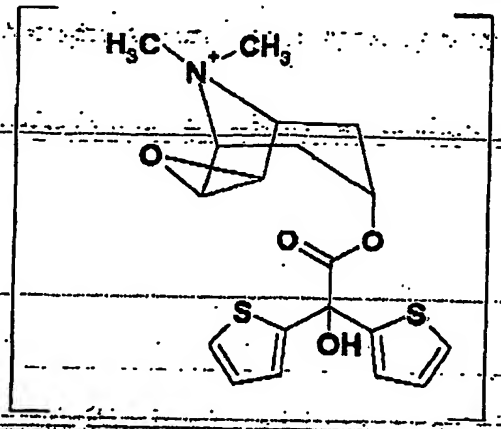


(1.4)

wherein X is a pharmaceutically acceptable anion.

A tiotropium salt (see EP 418716) has the structure of formula (1.5):

- 5 -



(1.5)

wherein X is a pharmaceutically acceptable anion.

Examples of suitable salt forms of ipratropium, oxitropium and tiotropium are fluoride, F^- chloride, Cl^-; bromide, Br^-; iodide, I^-; methanesulfonate, $CH_3S(=O)_2O^-$; ethanesulfonate, $CH_3CH_2S(=O)_2O^-$; methylsulfate, $CH_3OS(=O)_2O^-$; benzene sulfonate $C_6H_5S(=O)O^-$; and para-toluenesulfonate, $4\text{-}CH_3\text{-}C_6H_5S(=O)2O^-$. The bromide salt form is preferred.

Preferred combinations for use in the invention include:

- roflumilast and an ipratropium salt, particularly ipratropium bromide
- roflumilast and an oxitropium salt, particularly oxitropium bromide
- roflumilast and a tiotropium salt, particularly tiotropium bromide or tiotropium bromide monohydrate

It is understood that the active compounds and their pharmaceutically acceptable salts mentioned can also be present, for example, in the form of their pharmaceutically acceptable solvates, in particular in the form of their hydrates. Of particular importance in this connection is tiotropium bromide in form of its crystalline monohydrate as disclosed and described in detail in WO02/30928. The preparation of crystalline water-free tiotropium bromide is described in WO03/000265.

Respiratory diseases which may be mentioned are in particular allergen- and inflammation-induced bronchial disorders (bronchitis, obstructive bronchitis, spastic bronchitis, allergic bronchitis, allergic asthma, bronchial asthma, COPD), which can be treated by the combination according to the invention also in the sense of a long-term therapy (if desired with appropriate adjustment of the dose of the individual components to the needs at the time, for example needs subject to seasonally related variations). The combination is particularly useful in the treatment of COPD.

"Combined use" or "combination" within the meaning of the present invention is to be understood as meaning that the individual components can be administered simultaneously (in the form of a combination medicament – fixed combination), more or less simultaneously (from separate pack units – free combination) or in succession (directly in succession or else alternatively at a relatively large time interval) in a manner which is known per se and customary. As an example, one drug could be taken in the morning and one later in the day. Or in another scenario, one drug could be taken twice daily and the other once daily, either at the same time as one of the twice-a-day dosing occurred, or separately.

"Combined use" or "combination" within the meaning of the present invention is particularly to be understood as meaning that the two components act together in a synergistic manner.

"Use" in accordance with the invention is to be understood to mean topical application of the active compounds in inhalatory (orally and intranasally) or intranasally form. As suitable administration forms for inhalation may be mentioned inhalation powders, propellant-containing aerosols and propellant-free inhalation solutions. As suitable intranasal administration form may be mentioned, for example, the nasal spray.

Thus, the invention contemplates, for example, either co-administering both drugs in one delivery form such as an inhaler, which is putting both drugs in the same inhaler, or alternatively putting the both drugs in two different inhalers. Or, as a further alternative, administering one drug intranasally, for example in form of a nasal spray, and the other drug by inhalation.

The selective PDE4 inhibitors and the anticholinergic agents of the present invention may be conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurized container, pump, spray, atomizer (preferably an atomizer using electrodynamics to produce a fine mist) or nebulizer, with or without the use of a suitable propellant, e. g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,2,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide, a further perfluorinated hydrocarbon such as Perflubon [trade mark] or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered dose. The pressurized container , pump, spray, or nebulizer may contain a solution or suspension of the selective PDE4 inhibitor and/or the anticholinergic agent, e. g. using a mixture of ethanol (optionally aqueous ethanol) or a suitable agent for dispersing, solubilizing or extending release and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules, blisters and cartridges (made, for example, from gelatin or HMPC) for use in an inhaler or insufflator may be formulated to contain a powder mix of the selective PDE4 inhibitor and/or the anticholinergic agent of the invention, a suitable powder base, such as lactose or starch and a performance modifier such as l-leucine, mannitol or magnesium stearate.

Prior to use in a dry-powder formulation for inhalation selective PDE4 inhibitors and the anticholinergic agents of the invention will be micronised to a size suitable for delivery by inhalation (typically considered as less than 5 microns). Micronisation could be achieved by a range of methods, for example spiral jet milling, fluid bed jet milling or use of supercritical fluid crystallization.

A suitable solution formulation for use in an atomizer using electrohydrodynamics to produce a fine-mist may contain from 1 µg to 10 mg of an anticholinergic agent of the invention and the actuation volume may vary from 1 to 100 µl. A typical formulation may comprise an anticholinergic agent of the invention, propylene glycol, sterile water, ethanol and sodium chloride.

Aerosol or dry-powder formulations are preferably arranged so that each metered dose or "puff" contains from 1 to 4000 µg of an anticholinergic agent of the invention for delivery to the patient. The overall daily dose with an aerosol will be in the range from 1 µg to 20 mg which may be administered in a single dose or, alternatively, in divided doses throughout the day.

Typical formulations for intranasal administration include those mentioned above for inhalation and further include non-pressurized formulations in form of a solution or suspension in an inert vehicle such as water optionally in combination with conventional excipients such as buffers, anti-microbials, tonicity modifying agents and viscosity modifying agents, which may be administered by a nasal pump.

With respect to tiotropium bromide or tiotropium bromide monohydrate suitable tiotropium-containing powdery preparations for inhalative administration are disclosed in the international application WO02/30389. In the international application WO02/098874 inhalation capsules (Inhalettes) containing the active agent tiotropium in the form of a powder preparation are disclosed. Propellant-free inhalation formulations of tiotropium bromide or tiotropium bromide monohydrate are disclosed in the international applications WO02/36104 and WO02/36591.

For the above-mentioned prophylactic and therapeutic uses the dosages administered will, of course vary with the first and second active compound employed, the treatment desired and the disorder indicated.

The active compounds are dosed in an order of magnitude customary for the individual dose, it more likely being possible, on account of the individual actions, which are mutually positively influencing and reinforcing, to reduce the respective doses on the combined administration of the active compounds compared with the norm. For inhalation, ipratropium bromide is intended to be administered in a dose of preferably 1 to 3 mg per day by once, twice, three or four times daily administration; oxitropium bromide is intended to be administered in a dose of preferably 0.2 to 0.6 mg per day by once, twice or

three times daily administration; tiotropium bromide monohydrate is intended to be administered in a dose of 10 to 25 µg per day by once daily administration.

For inhalation, 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide (ROFLUMILAST) is intended to be administered in a dose of 100 µg to 1000 µg, preferably 250 µg to 500 µg per day, preferably by once daily administration.

For intranasal administration, 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide (ROFLUMILAST) is intended to be administered in a dose of 100 µg to 1000 µg, preferably 250 µg to 500 µg per day, preferably by once daily administration.

Patent claims

1. Pharmaceutical composition suited for topical administration, which comprises roflumilast and an anticholinergic agent selected from the group of ipratropium, oxitropium and tiotropium salts in a fixed or free combination.

2. Pharmaceutical composition according to claim 1, wherein topical administration means administration by inhalation.

3. Pharmaceutical composition according to claim 1, which is a fixed combination.

4. Pharmaceutical composition according to claim 1, which is a free combination.

5. A pharmaceutical composition according to claim 1, 2, 3 or 4 wherein the anticholinergic agent is tiotropium bromide or tiotropium bromide monohydrate.

6. A pharmaceutical composition according to claim 1, 2, 3 or 4 wherein the anticholinergic agent is ipratropium bromide.

7. A pharmaceutical composition according to claim 1, 2, 3 or 4, wherein the anticholinergic agent is oxitropium bromide.

8. A pharmaceutical composition according to any of claims 1 to 7, wherein roflumilast represents 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide.

9. A pharmaceutical composition according to any of claims 1 to 7, wherein roflumilast represents 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloro-1-oxypyrid-4-yl)benzamide.

10. Method for preventing or reducing the onset of symptoms of a respiratory disease, or treating or reducing the severity of a respiratory disease by administering to a patient in need thereof topically an effective amount of roflumilast and an anticholinergic agent selected from the group of ipratropium, oxitropium and tiotropium salts, either in a single combined form, separately, or separately and sequentially, where the sequential administration is close in time or remote in time.

11. Method according to claim 10, wherein topical administration means administration by inhalation.

12. Method according to claim 9 or 10, wherein the anticholinergic agent is tiotropium bromide or tiotropium bromide monohydrate.

13. Method according to claim 9 or 10, wherein the anticholinergic agent is ipratropium bromide.

14. Method according to claim 9 or 10, wherein the anticholinergic agent is oxitropium bromide.

15. Method according to any of claims 9 to 14, wherein roflumilast represents 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide.

16. Method according to any of claims 9 to 14, wherein roflumilast represents 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloro-1-oxypyrid-4-yl)benzamide.

Abstract

The invention relates to the administration of roflumilast and an anticholinergic agent selected from the group of an ipratropium, oxitropium or tiotropium salt for the treatment of respiratory diseases.